OF THE PRESENT APPLICATION

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CURATEK PHARMACEUTICALS LIMITED PARTNERSHIP

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54 TITLE OF INVENTION

INTRAVAGINAL TREATMENT OF VAGINAL INFECTIONS WITH BUFFERED METRONIDAZOLE COMPOSITIONS

Only the items marked with an "X" in the blocks below are applicable.

- ☐ THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2
- ☐ THE APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO. 21 01
- ☐ THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND BASED ON APPLICATION NO. 21 01

THIS APPLICATION IS ACCOMPANIED BY:

- ☒ 1. ~~A single copy of provisional~~ two copies of a complete specification of .....63... pages
- ☒ 2. Drawings of ..2..... sheets. (INFORMAL)
- ☐ 3. Publication particulars and abstract (Form P.8 in duplicate) (for complete only).
- ☐ 4. A copy of Figure .... of the drawings (if any) for the abstract (for complete only).
- ☐ 5. An assignment of invention.
- ☐ 6. Certified priority document(s) (State quantity) : .....
- ☐ 7. Translation of the priority document(s).
- ☐ 8. An assignment of priority rights.
- ☐ 9. A copy of the Form P.2 and the specification of S.A. Patent Application No. 21 01
- ☒ 10. A Form P.2 in duplicate.
- ☐ 11. A declaration and power of attorney on Form P.3.
- ☐ 12. Request for ante-dating on Form P.4.
- ☐ 13. Request for classification on Form P.9.
- ☐ 14. Request for delay of acceptance on Form P.4.
- ☐ 15.

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DATED THIS 7 DAY OF JUNE 19 90

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

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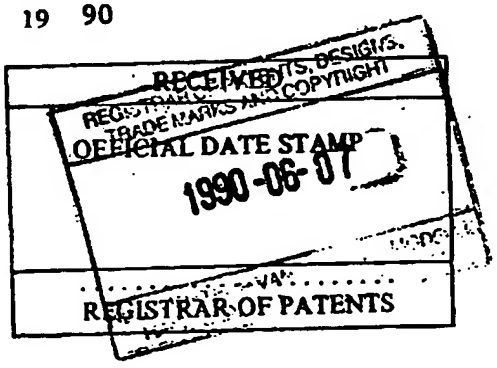

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TITLE OF INVENTION
54 INTRAVAGINAL TREATMENT OF VAGINAL INFECTIONS WITH BUFFERED METRONIDAZOLE COMPOSITIONS

A&A P207

[redacted] INTRAVAGINAL TREATMENT OF VAGINAL INFECTIONS WITH BUFFERED METRONIDAZOLE COMPOSITIONS

Cross-Reference to Related Application

~~This application is a continuation in part of my copending U.S. patent application, Serial No. 144,252, filed January 15, 1988.~~

Technical Field

This invention contemplates a method for intravaginal treatment of bacterial vaginosis and trichomoniasis with metronidazole formulations buffered to physiological vaginal pH.

Background of the Invention

Bacterial vaginosis (BV) is associated with an increased volume of vaginal discharge which has a foul, fishy odor. Vaginal pH is elevated from the normal range (pH 3-4) to values $\geq$ pH 4.7. The odor and elevated pH are caused by a high level of amines, most notably trimethylamine, in the vagina. These amines are volatilized when the pH is raised, for example, as with addition of KOH or interaction with semen. The vaginal discharge is homogenous in appearance as opposed to the flocculent discharge seen in Candida vaginitis. In contrast to candidiasis and trichomoniasis, itching generally is not associated with BV. A microscopic examination of a wet mount of the vaginal discharge in BV reveals an absence of polymorphonuclear leukocytes (PMNs). In contrast, the presence of many PMNs in a vaginal discharge is indicative of trichomoniasis, gonorrhea, or chlamydial cervicitis.

The causative organism for BV is a matter of some controversy. Gardnerella vaginalis is isolated from 98% of women with BV, but is also recovered in smaller numbers as normal flora in the vagina of

asymptomatic wom n in incidences as ...
et al, 1982).

In thos c nditions where Gardnerella is pr sent in high r concentrations, there is a significant decr ase in the numbers of Lactobacilli pr s nt compared to the normal vagina. The normal vaginal flora is compos d predominantly f Lactobacillus species, with an average pH of 4.0 (Hill and Embil, 1986; Bartlett and Polk, 1984). This low pH fosters growth and maintenance of the acidophilic Lactobacilli (anaerobic and facultatively anaerobic Gram-positive bacilli) that dominate the normal flora in concentrations of 10^8 to 10^9 Lactobacilli per milliliter of vagina secretions (Larsen and Galask, 1982; Rein, 1985). It is not known if a decrease in the Lactobacilli allows the Gardnerella to multiply, or if the increased numbers of Gardnerella actually inhibit the Lactobacilli. In any event, if the predominant microorganism present in the wet mount is not Lactobacilli, then BV must be suspected.

There have been overgrowths of other microorganisms seen in BV. Mycoplasma hominis and anaerobic bacteria including Bacteroides, Peptococcus, and Mobiluncus are also highly associated with BV (Eschenbach et al, 1988). In BV, G. vaginalis and the anaerobes can be present in overgrowths 1000 to 100,000 times more frequently than normal. It is also not known if the anaerobes are a result of the decreased amounts of Lactobacilli, or if they are responsible for the decrease. These organisms are present, however, in concentrations that should be considered pathogenic (Mead et al, 1986).

Characteristically seen in the wet mount in BV are abnormal cells termed "clue cells." These clue cells are vaginal epithelial cells with such a heavy coating of bacteria surrounding them that their

peripheral borders are obscured (Eschenbach et al. 1988).

Peters and Piot (1985) developed an experimental model of the G. vaginalis adherence to vaginal epithelial cells forming "clue cells." Using this model they found that the optimum pH for adhesion in vitro was pH 5 to 6 (the vaginal pH of women with bacterial vaginosis) and adhesion was limited at pH 3 to 4 which is the normal pH of vaginal fluid in women without vaginosis. If the same is true in vivo, a rise in vaginal pH is possibly a prerequisite in the pathogenesis of BV and perhaps precedes the formation of the pathognomonic "clue cells."

The antibacterial activity of Lactobacilli against other microorganisms has been suggested (Mardh and Soltesy, 1983). Skavin and Sylwan (1986) found that Lactobacilli strains inhibited growth of bacterial strains implicated in and isolated from women with BV in in vitro cultures. The bacterial strains tested included Mobiluncus mulieris, Mobiluncus curtisii, G. vaginalis, Peptococcus species, Peptococcus asaccharolyticus, Peptostreptococcus anaerobius, Gram-positive anaerobic coccus, and Bacteroides species. They also found that the lowest pH which would allow macroscopically visible growth of these bacterial strains ranged from pH 5.0 to 5.5. This data supports the importance of establishing and maintaining the presence of the Lactobacillus-dominated normal vaginal flora and the necessary pH environment for their growth and inhibition of other BV associated bacteria.

A clinical diagnosis of BV is made if three or more of the following four clinical criteria are present: (1) a homogenous discharge; (2) a pH $\geq$ 4.7; (3) a "fishy" amine odor upon the addition of 10% KOH to discharge; (4) presence of epithelial clue cells

epithelial cells (Eschenbach et al, 1988).

The efficacy of metronidazole in the treatment of BV as well as trichomoniasis is known. A marked effectiveness (essentially 100%) for metronidazole, given at 500 mg by mouth, twice daily for seven days has been demonstrated. Cure rates of 80-90% have repeatedly been reported since that time by the oral route of administration (Pheiffer et al., 1978; Balsdon et al., 1980; Eschenbach et al., 1983; Purdon et al., 1984; Charles et al., 1985; Swedberg et al., 1985; Malouf et al., 1981; Amsel et al., 1982; Hagstrom and Lindstedt, 1983; Mead et al., 1986). These studies employed the oral use of metronidazole in doses that ranged from 400 to 500 mg twice daily for three to seven days or 2 grams in a single dose. Heretofore, it has been generally accepted that the oral administration of metronidazole for five to seven days is the most effective way to treat BV; however, such a treatment for BV is not approved by the United States Food and Drug Administration (FDA). The Center for Disease Control recommends a dose of 500 mg of metronidazole given twice daily for seven days for treatment of bacterial vaginosis (CDC, 1985). Only one published paper reports the use of intravaginal metronidazole therapy for BV (Bistoletti et al., 1986). The authors compared the oral treatment which consisted of 400 mg of metronidazole twice daily for seven days to the application of a vaginal tablet containing 500 mg of metronidazole once daily for seven days.

The Merck Manual (15th edition, 1987) states on p. 244 that orally administered metronidazole provides effective female therapy when given at a single dose level of two grams, although the drug can be administered by injection.

The adverse reactions from [illegible]

of metronidazole can be extensive, however. For metronidazole, the "Modern Drug Encyclopedia" [A.J. Lewis, Editor, pub. by Vocke Medical Books, New York, N.Y. (1979)], contains the following statement on metronidazole:

> "Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis, stomatitis, leukopenia, dizziness, vertigo, incoordination, ataxia, convulsive seizures, numbness or paresthesia of extremities, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruption, weakness, urticaria, flushing, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, nasal congestion, proctitis, pyuria, and rarely, an unexplained darkening in the color of the urine have been reported. Flattening of the T wave may be seen in electrocardiographic tracings."

The need for providing safe and effective treatment for BV (without, for example, the side effects associated with the oral usage of metronidazole) assumes a more acute and pressing status when epidemiological trends and possible sequelae of a serious nature are given consideration. For example, vaginal infection with G. vaginalis, has been associated with possible sequelae, such as pelvic inflammatory disease, endometritis, and premature labor (Mead et al., 1986) that have an attendant, significant morbidity profile. Although there is no direct evidence linking BV with these conditions, it is not unreasonable to assume that an overgrowth of 10,000 to 100,000 anaerobic organisms in the vagina may result in certain genital diseases (Mead et al, 1986). Moreover, in the last decade there

has been a tendency towards a reduction in gen... trichomoniasis whil , during the same time span, there has been an increase in the so called "n n-sp cific genital dis ase" (Staerfelt et al, 1983). Furth r, BV may account for significantly more total vaginitis patients than either Candida or trichomoniasis (Mead et al, 1986).

Since BV is a localized problem, intravaginal application of metronidazole should in principle be clinically effective. Moreover, since in intravaginal application, unaffected organ systems would be subjected to significantly lower or non-detectable levels of metronidazole, its side effects would be therefore minimized or eliminated.

A desirable treatment for BV would be an intravaginal composition that delivers a minimum effective dose of metronidazole while it simultaneously adjusts and maintains the vaginal pH at about the normal physiological range.

An ideal treatment for BV would therefore be a formulation which would deliver an antimicrobial agent directly to the vagina while simultaneously adjusting and maintaining the vaginal pH to the normal physiological range.

Intravaginal metronidazole therapy for BV has been studied (Bistoletti et al., 1986). The authors compared oral treatment which consisted of 400 mg of metronidazole in the morning and evening for seven days to vaginal treatment consisting of the application of a vaginal insert containing 500 mg of the drug every evening for seven days. Thus, the total dose given was 5.6 g in the oral, and 3.5 g in the vaginal, treatment groups. The findings in the 38 patients who completed the study showed a cure rate, at four weeks after initiation of therapy, to be 15 out of 19 (79%) for the

vaginal treatment group and 14 out of 15 (...) ...
oral treatment. Cure was based on assessment of pH, vaginal discharge, the 10% KOH amine test, and examination of a wet smear for clue cells. These same authors also reported that lactate-producing microorganisms (Lactobacilli and aerobic Streptococci) were found more frequently after vaginal than after oral treatment and speculated that this difference may be due to the higher local concentration of the drug achieved by intravaginal administration. In this regard, a low concentration of metronidazole has been found in the vaginal fluid after a single oral dose of 2 g metronidazole (Davis et al., 1984). These authors concluded that topical administration of metronidazole might be more effective in re-establishing the normal microflora in the vagina. No side effects were reported related to the intravaginal use of metronidazole as the 500 mg insert. Although this study showed effectiveness of vaginally administered metronidazole, these researchers still used a high dose (3.5 grams) and made no attempt to adjust and control vaginal pH.

Like BV, Trichomonas vaginalis infections in symptomatic women cause complaints of abnormal discharge and odor in addition to pruritus, dyspareunia, or dysuria (Hager et al, 1980). Diagnosis requires identification of organisms by microscopic examination of the discharge, presence of a gray or yellow-green discharge, pH of discharge above 4.5, and a positive sniff test for odor producing volatile polyamines (McCue, 1989). An elevated vaginal pH encourages the growth of trichomonads. Foute and Kraus (1980) reported a vaginal pH above 4.5 to be associated and indicative of a trichomonal infection. Treatment generally consists of oral metronidazole therapy that is FDA

approved. Topical therapy is considered less effective, however. (Robbie & Sw et, 1983; McCue, 1989).

Where failure of treatment f a resistant case by oral metronidazole is encountered, a combination of oral and topical (vaginally applied) metronidazole has b en recommended (Fouts and Kraus, 1980). These authors r commend a total dose from 14 grams t as high as 42 grams of oral metronidazole combined with a 500 mg vaginal dose daily or every other day for up to 14 days. Clearly, an alternate to this extremely high dosing is desirable.

Because of low water solubility of metronidazole, various oil-based metronidazole compositions have been developed, which are generally either creams (oil in water emulsions) or ointments (petroleum jelly based compositions) with metronidazole being dissolved/suspended in the oil/water phases.

Romanian Patent No. 80,363, published November 30, 1982 (reported also at C.A. 101:116743c), describes a vaginal gel with antibiotic and anti-inflammatory activity. This gel comprises metronidazole, nystatin with other antibacterials selected from nitrofural, chloramphenicol, and tetracycline and camazulene or hexoestrol acetate incorporated into Carbopol 940™, a gel-forming polyacrylic acid polymer available from B.F. Goodrich, Cincinnati, Ohio.

Such gel formulation suffers from the disadvantage that it includes, in addition to metronidazole, various active antibiotic, antimicrobial and antimycotic agents. Such gel formulation then operates intravaginally on a broad spectrum "shot gun" basis to destroy not only the harmful bacteria associated with "vaginitis," but also the desirable bacteria, such as the Lactobacilli and other lactate-producing organisms (e.g., aerobic Streptococci) that

Romanian patent teaches a gel formulation for intravaginal use which is formulated at a pH of 6 to 6.5. H nc , us of such a vaginal gel formulation is pen to qu stion from the standpoint of being a safe treatment for BV or trichomoniasis since it leav s the treat d vagina in an abnormal condition where reinfection or inf ction by ther opportunistic microorganisms are possible sequelae.

A known commercial vaginal formulation of metronidazole currently on the international market for use as a trichomonacide, but not in the United States, is produced by Rhone-Poulenc Pharma Inc. of Montreal, P.Q., Canada. This formulation is a cream which contains 500 mg of metronidazole per application (5 grams). The recommended dose for trichomoniasis is one application once or twice daily for 10 to 20 days. Therefore, the total dose recommended ranges between 5 grams and 20 grams of metronidazole. The pH of this formulation was tested by an independent laboratory to be pH 6.1.

So far as known, no one has heretofore formulated or used metronidazole for intravaginal treatment at the physiological pH of the vagina (that is, a pH in the range of about 3 to about 4.25). In addition, no one has successfully treated BV or trichomonasis with less than multiple gram doses of metronidazole.

The need for a safe and effective treatment for vaginitis such as bacterial vaginosis and trichomoniasis which can eliminate the invading organisms at a low, safe dose and provide the necessary vaginal environment for growth and maintenance of lactate-producing organisms remains.

Summary of the Invention

The present invention provides a safe and effective, relatively low-dose treatment of a human vagina which is afflicted with BV or trichomoniasis, hereinafter collectively referred to as vaginitis. The invention also obviates the need for oral or intravenous administration of metronidazole for BV or for trichomoniasis, which administration can lead to undesirable side effects, as above reviewed.

A method aspect of this invention comprises introducing into such an afflicted vagina a therapeutically effective amount of metronidazole in a buffered pharmaceutical composition having a pH value in the range of about 3 to about 4.25, and preferably about 3.75 to about 4.25. The present method not only provides an effective relatively low-dose treatment of vaginitis, but also promotes the beneficial and effective re-establishment of the normal vaginal microflora, such as Lactobacilli and aerobic Streptococci. Thus, for example, the inventive method provides not only an effective vaginitis treatment, but also a safe treatment since it leaves the treated vagina in a normal condition able to cope with, and resist, future microorganism infections. So far as now known, no other existing vaginitis treatment offers such an advantage.

In accordance with another aspect of the present invention, a class of buffered metronidazole compositions is provided which is particularly well suited for the practice of such method. Buffered formulations of this class not only have the ability to control and eliminate, at surprisingly low dosages, the anaerobic bacteria population causing BV or the protozoan Trichomoniasis vaginalis that causes trichomoniasis, but also have the ability to adjust and

physiological pH. Thus, such compositions provide the necessary environment for the restoration of favorable bacterial flora while delivering a relatively low, but therapeutic amount of metronidazole.

The present compositions contain metronidazole as the sole active ingredient together with a buffer system in a physiologically tolerable medium. The buffer system is capable of providing a buffered pH value in the range of about 3 to about 4.25, preferably about 3.75 to about 4.25.

Presently preferred such compositions are aqueous gels that incorporate metronidazole, a gelled hydrophilic and water-dispersible polyacrylic acid polymer having free carboxylic acid groups, a buffer system, and an aqueous solvent for metronidazole and the buffer system.

A prolonged, substantially uniform and controlled release rate of metronidazole from the treating composition in the vaginal canal is provided by these compositions.

In a presently preferred mode of practicing this invention, a composition containing metronidazole as the sole active ingredient together with a buffer system capable of providing a buffered pH value in the range of about 3.75 to 4.25 is administered intravaginally to a patient afflicted with BV and/or trichonioniasis at a total dose rate of about 375 milligrams of metronidazole, administered in unit doses of at least about 20 milligrams each one to three times daily over a period of three to ten days. This dose is approximately ten-fold less than that previously employed for effective therapy with metronidazole. This reduced dose rate is believed to be related to the difference in pH adjustment and maintenance.

present invention will become readily apparent from the following description of the preferred embodiments of the invention, the accompanying examples, the drawings, and the appended claims.

Brief Description of the Drawings

In the figures forming a part of the disclosure:

FIG. 1 is a graph illustrating the buffering capacity of a gel composition of the type used in the practice of this invention when titrated with a relatively dilute strong base; and

FIG. 2 is a graph illustrating the buffering capacity of the gel composition of FIG. 1 when titrated with a relatively concentrated strong base.

Description of Preferred Embodiments

While this invention is susceptible to embodiment in many different forms, preferred embodiments of the invention are described hereinbelow in detail. It should be understood, however, that the present disclosure and the embodiments described herein are to be considered as exemplifications of the principles of this invention and are not intended to limit the invention.

The present invention is practiced by introducing into such an afflicted vagina a therapeutically effective amount of a buffered formulation of metronidazole, such as hereinbelow described and exemplified. The term "vagina" as used herein is intended to be inclusive of the vaginal region generally, including also the vulva and the cervix. Also, the term "afflicted vagina" or "vaginitis" as used herein is intended to be inclusive of bacterial vaginosis (BV), trichomoniasis, and the causative

protozoa, anaerobic bacteria, and mixtures ther of.

The quantity of metr nidazole intravaginally introduced as a single or unit dose can vary widely, depending upon many variables, such as the age and physical condition of the pati nt, th xtent of th pati nt's affliction, the frequency of administrati n, and th like.

The term "unit dose" or "unit dosage form" as used in the specification and claims refers to physically discrete units of such gel composition suitable for use as unitary dosages by human female subjects. Each unit contains a predetermined quantity of metronidazole calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The exact novel unit dosage form(s) of the invention to be used for any given patient is/are dictated by, and directly dependent on (a) the unique characteristics of the metronidazole compositions and the particular therapeutic effects to be achieved, and (b) the characteristics, especially the release rate of metronidazole from the particular composition contemplated for the intended therapeutic use, as disclosed in detail in the present specification, these being features of the present invention.

Any convenient unit dose form can be employed in practicing this invention. A presently preferred technique is to extrude a gel composition through a tubular applicator from a storage vessel, such as a syringe, squeezable tube, or the like, into the afflicted vagina. The volume of gel composition so contained within a single such vessel is conveniently and preferably selected so as to constitute a single dose, or two doses, or the like, so as to facilitate

patient. Th storage vessel is initially sealed, but is op ned at the tim of use. If more than a single dose is pres nt, th v ssel is pref rably resealable by a suitable closur means.

Another presently pref rred technique is to employ a single use packet (such as a small envelop - like structure, or the like) containing an intended single unit dose. The packet is initially sealed, but is opened at the time of use by tearing, cutting, or the like at a desired or planned location in the packet after which the packet is manually squeezed so that the contents are directly administrable as desired.

The dose or total quantity of metronidazole contained in a unit dose is typically at least about 20 milligrams (mg), and usually is not more than about 500 mg. A typical and presently preferred unit dose in a gel vehicle is in the range of about 20 to about 40 mg, in a cream vehicle about 50 mg to about 250 mg, and in a solid vehicle about 50 mg to about 250 mg.

Such a dose can be administered one to three times daily (that is, at spaced intervals in a 24 hour period) over a period of three to ten days. The total daily dose thus delivered can range from about 50 to about 500 mg. In a gel form of the composition, a daily dose of about 80 mg. is sufficient. When using other delivery media, a relatively higher daily dose of up to about 500 mg is preferred. The usual total dose for compositions of the present invention is in the range of about 300 mg to about 5,000 mg. A presently preferred administration procedure is to employ a unit dose of 5 grams of gel (delivering a dose of 37.5 mg of metronidazole) administered twice daily for a period of five days, thereby to deliver a total dose of about 375 mg. Those skilled in the art will appreciate that the

that higher and low r dose lev ls can b employed without departing from th spirit and scope of the present invention.

Such doses are significantly low r than the comparable 7 gram dos (500 mg b.i.d. employed for 7 days, the standard BV dosag) as curr ntly utilized and recomm nd d by CDC. The low daily dose of th particularly preferred gel composition directly applied to the site of activity decreases the risks of dose related side effects and potential systemic activity. The effectiveness of this novel, low dose therapy is believed to be related to the combination of site specificity, controlled release, pH adjustment, control of vaginal environment, and provision for reestablishment of necessary normal vaginal flora, i.e., lactate producing organisms.

The active ingredient in the present composition is 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole). This drug is described in U.S. Patent No. 2,944,061 to Jacob et al., and is commercially available.

The term "metronidazole" as used in this specification and claims includes not only 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, but also those analogs and derivatives of metronidazole (salts, esters, etc.) which are soluble in the aqueous or oil phases of the compositions described herein and which exhibit therapeutic activity when applied as taught by the present invention. A physiologically tolerable medium is utilized as the delivery vehicle for metronidazole.

The term "physiologically tolerable medium" as used herein refers to one or more viscous-to-solid materials which are non-irritating to the vaginal region. While a given such medium in a presently

material, a plurality of components can comprise such a medium as well. Examples of components include water, oil, surfactants, preservatives, penetration enhancers, preservatives, and the like, such as hereinbelow described and illustrated. For purposes of avoiding problems of pooling and running the physiologically tolerable medium is preferably characterized by a viscosity at ambient conditions (e.g., 25°C, 760 mm Hg) with said metronidazole and also said buffer system dissolved and/or dispersed therein which is at least sufficient to maintain a product composition of this invention in a non-flowable state.

The term "buffer system" or "buffer" as used herein has reference to a solute agent or agents which, when in water solution, stabilize such solution against a major change in pH (or hydrogen ion concentration) when acids or bases are added thereto. Solute agent or agents which are thus responsible for a resistance to change in pH from a starting buffered pH value in the range above indicated are well known.

For example, a pH of 4.024 can be obtained with a solution of 0.05 M acid potassium phthalate. Similarly, a pH value of about 4.0 can be achieved with an acetic acid-sodium acetate buffer. Also, a pH value of about 4.0 can be achieved with, for example, 50 ml of 0.1 molar potassium hydrogen phthalate plus about 0.1 ml of 0.1 M HCl, and a pH value of about 4.1 can be achieved with, for example, 50 ml of 0.1 M potassium hydrogen phthalate plus about 1.3 ml of 0.1 M NaOH. Various other buffers for achieving the desired pH values are also available, for example, DL-valine (pH 4.0), and the like. Virtually any pharmaceutically acceptable buffer system can be used which will achieve a pH in the range indicated for topical applications.

suitable for vaginal introduction in accord with the present invention and suitable for achieving the desired therapeutic action and desired physiological pH of the vagina can be in any convenient form, such as suspensions; mulsions; clear and paqu gels; semisolid systems, including intments, pastes, oil-in-water (o/w) creams, semisolid emulsions with solid internal phases, semisolid emulsions with fluid internal phases, gels, and rigid foams; vaginal suppositories; tablets (inserts); and the like.

Buffered metronidazole composition vehicles suitable for use in practicing this invention may be classified as follows:

1. Oleaginous compositional bases or ointments that are all oil, e.g., petrolatum and mineral oil systems
2. Absorption compositional bases
   a. Anhydrous oleaginous systems which absorb water
   b. Water-in-oil (w/o) emulsion systems, e.g., aquaphor
3. Emulsion compositional bases of the water-in-oil (w/o) type
4. Emulsion compositional bases of the oil-in-water type (o/w)
5. Anhydrous water soluble compositional bases
6. Aqueous solutions or suspensions, with or without hydrogels as a viscosity enhancer
7. Suppositories/inserts

Each of the above indicated drug delivery vehicles is known in the art; however, for exemplary purposes of preparing compositions for use in the

practice of this invention.

descriptions are provided:

1. Oleaginous Bases or Ointments:

This class of formulations comprises metronidazole and hydrocarb n-based semisolids containing dissolved and/or suspend d bact ri stats/pr servatives and a buffer system. The petrolatum component in thes bases can b any paraffin ranging in viscosity from mineral oil employing incorporated isobutylene, colloidal silica, or stearate salts to paraffin waxes. White and yellow petrolatum are examples of such systems. Bases of this class can be made by incorporating high-melting waxes into a fluid mineral oil via fusion or by incorporation of polyethylene into mineral oil at elevated temperature. Polysiloxanes (also known as silicones) are suitable for use in these bases and typically have a viscosity in the range of about 0.5 to 10^6 centistokes. The organic entities attached to the polysiloxane are preferably lower molecular weight hydrocarbon moieties having from 1 to 8 carbons each, such as lower alkyl, lower alkenyl, phenyl and alkyl substituted phenyl, and phenyl(lower)alkyl, such as benzyl. In such a moiety, each lower alkyl or alkenyl group preferably has 1 to 3 carbons inclusive, such as in a dimethylsiloxane polymer. A specific formulation for an oleaginous system is illustrated in the examples below.

2. Absorption Bases:

Absorption bases used for these buffered formulations can be oleaginous systems which contain, in addition to metronidazole, ingredients with the capacity to emulsify a significant quantity of water. Water-in-oil (w/o) emulsions can be formed wherein the external phase is oleaginous in character.

Preservatives/bacteriostats, such as the parabens,

bases as emulsifi d aqueous solutions together with the active ingr dient. Diverse additiv s are conveniently used as the emulsifier, and th se include, but ar not limited t , cholest rol, lan lin (which contains cholesterol and cholesterol esters and other emulsifiers), lanolin d rivatives, be swax, fatty alcoh ls, wool wax alcohols, low HLB (hydrophobe/lipophobe balance) emulsifiers, and assorted ionic and nonionic surfactants, singularly or in combination.

3. Water-In-Oil (W/O) Emulsion Bases:

These formulations can be an expansion of the general class of absorption bases which are liquids or creams. They can be prepared by taking a mixture of metronidazole with oil phase ingredients, bacteriostats/preservatives and buffer salts which are dissolved or suspended therein and to which water has been added to form a water-in-oil emulsion.

Compositions shown in the examples below are provided as being exemplary of these systems, but those skilled in the art will appreciate that substitutions, additions, and/or omissions of the specified components can be made. A listing of alternate components that could be incorporated in these examples is provided hereinbelow.

4. Oil-In-Water (O/W) Emulsion Bases:

These systems are semisolid emulsions, micro-emulsions, or foam emulsion systems containing metronidazole. Usually such a system has a "creamy white" appearance. Typically, the internal oil phase is in the range in percentage composition of about 10% to about 40% oil by weight and the external phase may contain 80% or more water. The oleaginous phase may contain, but is not limited to, long-chain alcohols

palmitates, stearates), long-chain acids (palmitic, stearic), vegetable and animal oils and assorted waxes. These can be made with anionic, cationic, nonionic or amphoteric surfactants, or with combinations especially of the nonionic surfactants. The examples below are exemplary of these systems, but those skilled in the art will appreciate that substitutions and additions or omissions of the specified components could be made by one who is skilled in the art. A listing of alternate components is provided below.

5. Anhydrous Water Soluble Bases:

These systems include solutions or suspensions of metronidazole and the desired buffer system in glycols, such as glycerin, polyethylene glycol, propylene glycol which are thickened with hydroxypropyl cellulose.

The examples below are provided as being illustrative of these systems. Those skilled in the art will appreciate that substitutions, additions and/or omissions of the specified components can be made. A listing of alternate components that could be incorporated in these composition examples is provided below.

6. Aqueous Solutions or Suspensions:

These systems can be prepared using metronidazole with or without hydrogels as a viscosity-enhancing additive. When there is no viscosity building agent present, such a composition can be prepared as a douche that is essentially a solution or suspension of metronidazole and buffer components in water. This class of vehicles can preferably also include micellar solubilized metronidazole along with a buffer system employing water plus a relatively high HLB surfactant.

gels made with gelling agents. Some examples of th se gelling agents are:

Cellulosics -	Methyl cellulose, carboxymethyl cellulose, hydroxyethyl c llulos , and hydroxypropyl c llulose.
Cationic Polymers -	"Polyquat rnium-10", a polymeric quaternary ammonium salt of hydroxyethyl cellulose reacted with a trimethyl ammonium-substituted epoxide, and the like.
Polyoxyalkylenes and derivatives thereof -	polyoxyethylene/polyoxypropylene esters of lanolin.
Carboxyvinyl polymers -	cross-linked acrylic acid polymers, e.g., those commercially available from B.F. Goodrich Co., Akron, Ohio, under the designation CARBOPOL™.

7. Vaginal Inserts and Suppositories:

Suppositories containing metronidazole can be, for example, oleaginous in nature which melt at body temperature, or polyethylene glycol-based which dissolve in the vaginal fluids. Additional bases for suppositories are glycerin and glycerinated gelatin. Alternately, solids such as beta-lactose, metronidazole, and buffer system components can be compressed into tablets which after insertion dissolve, thereby releasing the buffered metronidazole system.

but those skill d in th art will appreciate that substitutions, additions and/or omissi ns of the specifi d components can be made. A listing below exemplifies alternate components that could be incorporat d in these examples:

Surfactants

As above indicated, the buffer d formulations of this invention can contain one or more surfactants. Suitable surfactants include anionic, cationic, amphoteric and nonionic surfactants which are pharmaceutically acceptable in topical applications. Any one or more surfactants having the above characteristics can be used. Representative examples of suitable surfactants which can be used in the formulations of this invention are described in Martin and Cook, Remington's Practice of Pharmacy, 12th edition, 1961, pp. 219-226, R.G. Harry, Cosmetics: Their Principles and Practices, (1965), pp. 396-398 and 413-417, and E. Sagarin, Cosmetics Science and Technology, (1957), pp. 328-333, 1060-1063 and 1254, which publications are herein incorporated by reference. Representative surfactants which are suitable include:

A. Anionic agents

1. Sodium, potassium and ammonium soaps derived from fatty acids having from 10 to 22 carbon atoms; and polyvalent metal (magnesium, calcium, zinc, aluminum and lead) soaps derived from fatty acids having from 10 to 22 carbons.

2. Amine soaps derived from fatty acids having from 10 to 22 carbons and primary, secondary and tertiary amines, such as monoethanolamine, diethanolamine and triethanolamine, and cyclic amines, such as morpholine. An examples is triethanolamine stearate, or the like.

rosin acids, .g., abietic acid.

4. Alkali m tal salts f sulfate compounds which can be r presented by the formula $ROSO_3H$ wherein the R group repr s nts an organic moiety, such as, for example, a fatty alcohol residue having up to 22 carbons. Exampl s includ sodium lauryl sulfate, sodium c tyl sulfate, sodium monolauryl glyceryl sulfate, an oil such as sulfated castor, olive, teaseed, neat's foot cottonseed, rape seed, corn and rice, oil, and the like.

5. Alkali metal salts of sulfonated compounds which can be represented by the formula RSO_3H wherein the R group can have from 8 to 22 carbons. These include alkane sulfonates, such as dioctyl sodium sulfosuccinate, oxyethylated alkylaryl sulfate, alkyl aromatic sulfonates such as sodium isopropylnaphthalenesulfonate, sodium dodecylbenzenesulfonate, sodium sulfonaphthylstearate, and the like.

B. Cationic agents

1. Amine salts (e.g., hydrochlorides and acetates) derived from straight chain fatty amines having from 8 to 18 carbons. An example is octodecylamine hydrochloride, and the like.

2. Quaternary ammonium salts formed by alkylation of fatty amines with methyl chloride, dimethylsulfate, benzylchloride, and the like. These compounds can be represented by the formula [RR'R''R'''N]Y wherein each of R, R', R'', R''' is a long chain aliphatic group of from 8 to 22 carbons or a fatty acid amide residue; a short aliphatic group, such as methyl, ethyl, or propyl, an aromatic group, such as a phenyl or benzyl radical; or a heterocyclic group, such as pyridine or piperidine residue; and Y represents an inorganic or lower organic cation, such as chloride,

triethanolamine stearat , cetyl trimethyl ammonium bromide, b nzalkoniumchl rid , and th lik .

C. Nonionic agents

1. Ethers, such as cond nsation products of alkylphenols with from 6 to 20 moles of ethylene oxide, such phenols being monoalkylated, dialkylated r polyalkylat d with alkyl side chains having from 5 to 18 carbons each, and the corresponding naphthalene or diphenyl compounds. Examples include polyoxyethylene, polyoxyethylene-polyoxypropylene copolymers, and the like.

2. Esters, such as compounds which can be represented by the formula RCOOR' wherein R is a long hydrocarbon chain derived from a fatty acid having from 12 to 22 carbons, and R' is derived from a polyhydric alcohol. Examples include glyceryl monostearate, diethylene glycol monolaurate, sorbitan fatty acid esters derived, for example, from lauric, palmitic, stearic and/or oleic acids, and the like.

3. Ether-esters wherein polyoxyethylene chains are found with an unreacted hydroxy group of esters of fatty acids and polyhydric alcohols.

4. Fatty acid amides, such as lauroyl diethanolamide and the like.

D. Ampholytic agents

1. Surfactants, such as those having amino and carboxy groups. Examples include dodecyl B-alanine, imidazoline derivatives such as the so-called "Miranols", and the like.

2. Surfactants containing amino and sulfuric acid or sulfonic acid groups formed by condensing an alkanesulfonamide with formaldehyde and methyltaurine.

above indicated four general classes includ sorbitan triol ate, sorbitan trist arate, sorbitan sesquiol ate, glycerol monostearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan monolaurat , polyoxy thylene lauryl ether, polyethylene glycol 400 monostearat , tri thanolamine oleate, polyoxy thyl ne glycol 400 monolaurate, polyoxyethylene sorbitan monostearate, polyoxyethylenesorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, potassium oleate, sodium lauryl sulfate, lauroyl imidazoline, sodium dodecylbenzene sulfonate, sodium monoglyceride sulfate, sodium alkaralkyl polyglycol sulfate, sodium oleyl taurate, sodium dioctyl sulfosuccinate, lauryl polyglycol, ether, sodium dibutylnaphthalenesulfonate, alkyl phenol polyglycol ether, sorbitan monolaurate polyglycol ether, sulfonated castor oil, tall oil polyglycol ester, alkyl dimethyl benzylammonium chloride, alkyl naphthalene pyridinium chloride, cetyl dimethyl ethylammonium bromide, alkyl dimethyl chlorobenzylammonium chloride, dibutyl phenyl phenol sulfonate, ester of colaminoethylformyl methyl pyridinium chloride, sulfonated methyl oleylamide, sorbitan monolaurate polyglycol ether, polyglycol oleate, sodium lauryl sulfoacetate, sodium 2-ethylhexanol sulfate, sodium 7-ethyl-2-methylundecanol-4 sulfate, sodium 3,9-diethyltridecanol-6 sulfate, sodium lauryl and myristyl collamide sulfonate and N-(sodium sulfoethyl) oleamide, and the like.

Preservatives

As above indicated, the buffered compositions of this invention can contain suitable bacterostats, preservatives, inhibitors, or the like, such as methyl, ethyl, propyl, and butyl esters of parahydroxybenzoic acid, propyl gallate, sorbic acid and its sodium and

sodium salts, "Dioxin" (6-acetoxy-2,4-dimethyl-m-dioxane), "Bronopol" (2-brom -2-nitropropane-1,3-diol) and salicylanilides such as disbromosalicylanilide, tribromosalicylamilides, "Cinaryl" 100 and 200 or "Dowicil" 100 and 200 (Cis isom r of 1-(3-chloroallyl-3,5,7-triaza-1-azanidadamantan chl ride), h xachlorophene, sodium benzoate, citric acid, thylene diaminetetraacetic acid and its alkali metal and alkaline earth metal salts, butyl hydroxyanisol, butyl hydroxytoluene, phenolic compounds such as chloro- and bromocresols and chloro- and bromo- oxylenols, quaternary ammonium compounds like benzalkonium chloride, aromatic alcohols such as phenylethyl alcohol, benzyl alcohol, etc., chlorobutanol, quinoline derivatives such as iodochlorhydroxyquinolin, and the like.

Hydrophilic and Hydrophobic Thickeners

(Suspending, gelling, or viscosity inducing agents)

Suitable thickeners which may be used in the composition of this invention include colloidal alumina, colloidal silica, alginic acid and derivatives thereof, "Carbopols" (carboxyvinyl polymers), cellulose derivatives, such as "Klucel" (cellulose ethers), Methocel (methyl cellulose), "Natrosol" (hydroxyethyl cellulose), sodium carboxymethyl cellulose, gelatin, natural gums, such as agar, tragacanth, acacia gum, guar gum, stearates, isobutylene, waxes, carrageen, and the like, egg yolk, lecithin, pectin, thixcin, resins like ethyleneoxide polymers, such as the so called polyoxes, and the like.

Other Adjuvants/Cosolvents

Other adjuvants which can be incorporated into a composition of this invention includes waxes, such as beeswax, spermaceti, paraffin waxes, and fatty acids,

the like.

Monohydric alcohols can be used, such as those having from 1 to 22 carbons per molecule, such as methanol, ethanol, propanol, isopropanol, butanol, hexanol, cetyl alcohol, stearyl alcohol, and the like.

Dihydric and polyhydric alcohols can be used, such as those having from 2 to 22 carbons per molecule, such as propylene glycol, glycerin, hexanetriols, such as 1,2,6-hexanetriol, sorbitol, 1,3-butanediol, 2,3-butanediol, and the like.

Polyethylene glycols and polypropylene glycols can be used, such as those having molecular weight in the range of about 100 to about 20,000.

Esters of aliphatic monobasic and dibasic acids can be used, such as those having from 2 to 22 carbons per molecule, with (a) monohydric alcohols having from 1 to 20 carbons per molecule, (b) di- and polyhydric alcohols having from 2 to 20 carbons per molecule, and (c) sugar alcohols. Examples include isopropyl myristate, myristyl myristate, cetyl stearate, methyl stearate, isopropyl sebacate, methyl sebacate, sucrose monolaurate, sucrose monostearate, and the like.

Sterols, such as cholesterol, and the like.

Buffers

In general, and as above indicated, buffers for the present compositions include any physiologically acceptable organic acid (and its corresponding salt), either liquid or solid (depending upon application), having a pKa around 3 to 5 including, but not limited to, acetic, fumaric, lactic, citric, propionic, lactic, malic, succinic, and tartaric acids.

Gases

Compositions of this invention can contain air or some other medically/pharmaceutically/cosmetically

Illustrative Buffered Compositions of Metronidazole

A composition of the invention advantageously comprises, in general, at least about 0.1 weight percent metronidazole, based on the total weight of the composition. Preferably metronidazole is present in an amount of about 0.25% to about 1.0%, and more preferably about 0.75% by weight, based on the total weight of the composition. Typically, a composition contains not more than about 3 percent metronidazole. Larger and smaller contents of metronidazole can be used without departing from the spirit and scope of this invention.

Substantially oil-free, aqueous compositions containing metronidazole, in which this drug is solubilized in a single-phase aqueous gel, are a preferred class of embodiments used in the practice of this invention. The overall advantages of such aqueous gel compositions in treating BV have been discussed above, and are presented and illustrated in greater detail hereinbelow.

The actual concentration of metronidazole in any given such composition may vary, depending on variables such as the nature and degree of the BV being treated, the duration of the therapeutic treatment period contemplated, the size of the particular unit dose to be administered, and the like.

In the preferred compositions, metronidazole is in an aqueous solution of a high molecular weight polycarboxylated vinyl polymer. The polymer imparts a desirable viscous, gelled consistency to the composition when mixed with metronidazole and water. The preferred gel compositions contain at least about 95% by weight water, based on the total weight of the composition, and have the requisite degree of metronidazole concentration, and hence thermodynamic activity, for

metronidazole in the vaginal [illegible]
compositions also have the requisite therapeutic activities as previously described.

The gel-forming polymer useful in compounding such preferred compositions may be any suitable polymer which is hydrophilic and water-dispersible, has free carboxylic groups and relatively high base binding capacity, and forms a buffered gel of substantially uniform consistency when neutralized with a base. Preferred polymers for use in the compositions of the invention are water-dispersible, polycarboxylated vinyl polymers. Polyacrylic acid polymers are particularly preferred for the present purposes. The molecular weight of the polymer is desirably in the range of about 1,250,000 and about 4,000,000 daltons. Suitable polyacrylic acid polymers include, but are not limited to, polyacrylic acid polymers slightly cross-linked with a polyalkenyl polyether, such as those commercially available from B.F. Goodrich, Cincinnati, Ohio, under the trademarks Carbopol 934, 940, 950 and 941. Carbopol 934P™ is a particularly preferred polymer for use in practicing this invention.

The polymer is present in an amount sufficient to cause gelling of a preferred composition, and to impart the desired viscous consistency to the resulting topical formulation. In addition and importantly, the polymer is used in concentrations that afford the buffering capacity and pH range that are necessary for this method. The metronidazole compositions advantageously comprise about 0.2% to about 7.0% by weight of the polymer, preferably about 0.5% to about 2.5%, and most preferably about 2.0% by weight of the polymer based on the total weight of the composition.

Aqueous solutions of these polymers form gels when neutralized with a base. Water-soluble bases which

such as an aqueous solution of ammonia, NaOH, and organic amines, e.g., alkylamines, such as methylamine and ethylamine, dialkylamines, trialkylamines, alkanolamines, dialkanolamines, and the like. Preferably a strong base is employed. The pharmaceutically effective component of the compositions of the present invention, metronidazole, is its self sufficiently basic to partially neutralize the acidic polymer in aqueous solution to the desired degree and to promote gelling.

Optionally, a preferred gel composition may further include a solubilizer, i.e., an agent that promotes penetration of the active drug into the microorganisms. Such solubilizers include, but are not limited to, dimethyl sulfoxide (DMSO) and propylene glycol, with the latter being preferred. The composition advantageously includes about 1.0% to about 50%, preferably about 2% to about 5%, and more preferably about 3% by weight, of such solubilizer, based on the total weight of the composition.

Preservatives optionally may be incorporated into such gel compositions in an amount effective for inhibiting growth of microbes, such as yeast, molds, and bacteria during gel composition storage. Any conventional preservative may be used, with parabens being preferred. A mixture of methyl paraben and propyl paraben has been found to be particularly effective as a preservative. Most preferably, such a composition comprises about 0.08% by weight of methyl paraben and about 0.02% by weight of propyl paraben based on the total weight of the gel composition.

Ethylenediaminetetraacetic acid (EDTA) or one of its salts is commonly added to dermatological preparations, and may optionally be incorporated into

may be present in the formulation, which is useful because some patients have adverse reactions to preparations containing metal impurities. The EDTA will also inhibit undesirable "browning" of the composition which may occur over time in compositions having a low pH value, e.g., a pH value of about 3.0 to about 4.5. Advantageously, a gel composition optionally further includes from about 0.01% to about 0.1%, preferably about 0.05% by weight, of EDTA based on the total weight of the composition.

The final pH value of a gel composition may vary within a physiologically compatible range. Advantageously, the final pH value is a physiologically compatible, i.e., not harmful to biological tissue, adjusts and controls vaginal environment to normal, healthy range and is acidic. The pH value is about 3 to about 4.25, and preferably about 3.75 to 4.25. Any suitable method of adjusting the pH value of aqueous solutions may be used. Advantageously, sodium hydroxide (NaOH) is added to the composition to bring the final pH value to the desired level. The gel compositions are more viscous at pH values that approach neutrality than at the more acidic pH values within the preferred range, i.e., viscosity increases as the polymer in the gel is neutralized to a greater degree, e.g., with NaOH.

The ingredients listed above may be combined in any order and manner that produces a composition comprising metronidazole dissolved in, and evenly dispersed throughout, a one-phase aqueous gel of the desired consistency and pH value. One suitable method of preparing such compositions involves preparation of an aqueous solution of the polymer, which will be called "Part A". Advantageously, this solution comprises the polymer in distilled water. A "Part B" is prepared comprising metronidazole. Mixing of Parts A and B

in Part B. If EDTA is to be added to th formulation, it is preferably included in Part A. The pH value may then b adjusted to th desired l v l, e.g., by addition of NaOH.

The resulting homog neous buffered gels having a pH in th range indicat d possess the advantageous properties described above, including utilizing non-inflammatory and non-irritating ingredients. Higher specific activity of metronidazole results due to increased diffusion across membranes, release from the vehicle, and controlled pH. The result is greater therapeutic effectiveness using smaller amount of metronidazole. A formulation has a desirable consistency that prevents undesirable pooling and leaking of metronidazole. High concentrations of tissue-drying ingredients (e.g. alcohols and acetone), which are found, for example, in some preparations to promote drug solubility, are also avoided. Such ingredients at high concentration may excessively dry the patient's vaginal wall causing undesirable discomfort.

As indicated above, when such above described gel composition is introduced as described into an afflicted vagina, a prolonged and surprisingly uniform and regulated (controlled) release rate of metronidazole from the gel composition into the environment of the vagina is achieved. Pooling and running is minimized. The release rate or delivery is sustained for an extended period of time.

The release rate is such that the quantity of the drug which is delivered to vaginal tissues during the release period is at, or slightly above, a minimum therapeutically effective level.

very useful buffering capacity which, in addition to, and in coaction with, the desired bactericidal activity of the metronidazole, is desirable and important in achieving the therapeutic effectiveness that is associated with the practice of this invention. This combination allows for the therapeutic effectiveness of the novel low dose metronidazole formulation by adjusting and controlling the pH of the vaginal environment.

Thus, the gel compositions, as is characteristic of a buffered composition of the invention generally, resist changes in pH upon exposure in the use environment to an acid or a base. In the preparation of a gel composition as above explained herein, a strong base (e.g., sodium hydroxide) is preferably added to the Carbopol™ polymer (weak acid form). This neutralization thickens the formulation to produce the desired gel consistency. It also produces the mixture of components needed to produce a buffered system.

As the exemplary material hereinbelow presented indicates, when a portion of a gel formulation is titrated by a strong base (e.g., sodium hydroxide) successively using each of a concentrated solution of the base and a dilute solution of the base, such that the total volume of base is substantially increased (for example, doubled), it is found not only that there is a significant buffering effect inherent in the gel formulation, but also that there is very little effect on the gel formulation buffer strength as a result of dilution.

These results are significant for purposes of accomplishing topical treatment of, for example, BV by the practice of this invention. For one thing, these results show that the inherent dilution of a unit dose

prevent and to treat the und sirable alkalinization of the vaginal tissue caused by infections of the BV type. For anoth r thing, thes r sults show that vaginal tissue can b promoted t remain at a pH below about 4.5 which is desirable t inhibit BV organism activity, and t promote c rtain desirable and normal bacterial colonization and d velopment, such as Lactobacilli, and the like. For still another thing, these results show that the prolonged release rate characteristics associated with the gel composition in the vagina are largely unaffected by unit dose dilution.

The practice of the present invention is demonstrated in the following examples. These examples are meant to illustrate the invention rather than to limit its scope. Variations in the treating compositions which do not adversely affect the effectiveness of metronidazole will be evident to one skilled in the art, and are within the scope of this invention. For example, additional ingredients such as coloring agents, and the like may be included in the compositions as long as the resulting composition retains desirable properties, as described above. Unless otherwise indicated, each composition is prepared by conventionally admixing the respective indicated components together. Also, unless otherwise indicated, each composition is prepared using a buffer (buffer system) which in use provides a pH value in the range of about 3 to about 4.25.

EXAMPLE 1: Gel Preparation

A 30 kilogram batch of a composition of the present invention was prepared as follows. 600 grams of Carbopol 934P™ (2.0% by weight of the final weight of

distilled water containing 15 grams of ethylenediaminetetraac tic acid (EDTA) dis dium dihydrat . Sufficient amount of 10 weight percent sodium hydroxide (NaOH) solution was added to bring the pH value to about 3.75 to 3.9. This aqu ous polymer solution was called "Part A". "Part B" was prepared by mixing 900 grams of propylene glyc l (3% by weight of the final weight of the composition), 24 grams of methyl paraben (0.08% by weight of the final weight of the composition) and 6.0 grams of propyl paraben (0.02% by weight of the final weight of the composition). The mixture was added to 225 grams of metronidazole dispersed in 11.4 liters of distilled water maintained at 50 C. Parts A and B were then mixed thoroughly and gelling of the composition resulted. A cold aqueous solution of NaOH was then used to adjust the final pH value to 4.0. Distilled water was then added to give the desired 30 kilogram final weight. The NaOH and water were thoroughly mixed into the viscous gel.

EXAMPLE 2: Oleaginous System Based on Mineral Oil

Ingredient	Wt %
Metronidazole	0.5 - 10
Colloidal silica	5.0
Alpha-Tocopherol	0.1
Tartaric acid/sodium tartrate	2
Mineral oil 70/80 cps (q.s.)	100

An embodiment of this formulation is prepared by slurrying the metronidazole in the mineral oil and admixing the remaining components therewith.

Ingredient	Wt %
Metronidazole	0.5 - 10
"Aquaphor"*	50
Methyl Paraben	0.1
Propylen Glyc 1	3 - 5
Buffer salts	10
Water (q.s.)	100

* "Aquaphor" is a trademark of Beiersdorf, Inc., Norwalk, CT for a brand of hydrophilic petrolatum.

EXAMPLE 4: Water-in-Oil (W/O) Emulsion Systems

W/O Composition I

Ingredient	Wt %
Oleth-3*	3.0
Metronidazole	0.5 - 10
Buffer salts	5 - 10
Laneth-5**	5.0
Mineral Oil 70/80	12.0
Glycerin	4.0
Methyl Paraben	0.1
Propyl Paraben	0.1
Water (q.s.)	100

* "Oleth-3" is the polyethylene glycol ether of oleyl alcohol having an average ethoxylation value of 3.

** "Laneth 5" is the polyethylene glycol ether of lanolin alcohol having an average ethoxylation value of 5.

Ingredient	Wt %
Cholesterol	1.5
Beeswax	4.0
Stearyl Alcohol	1.5
Petrolatum	43.0
Metronidazole	0.5 - 10
Propylen Glycol	5 - 10
Acetate Buffer, pH 4.0	10
Imidazolidinyl urea	0.1
Water (q.s.)	100

EXAMPLE 5: Oil-In-Water O/W Emulsions

O/W Composition I

Ingredient	Wt %
Metronidazole	0.5 - 10
Mineral Oil	20
Cetyl Alcohol	2
"Polawax"*	4
Glycerin	5
Methyl Paraben	0.1
Propyl Paraben	0.05
"Carbopol 934P"**	0.5 - 2
NaOH solution 10% q.s.	pH 3.0 - 4.5
Water (q.s.)	100

* "Polawax" is a trademark of Croda, Inc., New York, N.Y. for a brand of emulsifying wax.

** "Carbopol 937-P" is a trademark of B.F. Goodrich Co. for a brand of acrylic acid polymer crosslinked with a polyfunctional agent.

Ingredient	Wt %
Metronidazole	0.5 - 10
P trolatum	5.0
Cetyl Alcohol	5.0
Sodium Lauryl Sulfate	0.3
Methyl Paraben	0.1
Propyl Paraben	0.1
Acetate Buffer, pH 4.0	10
Glycerin	5
Water (q.s.)	100

O/W Composition III
(Transparent Microemulsion)

Ingredient	Wt %
Metronidazole	0.5 - 10
"Laneth-15"*	30
Isopropyl Myrestate	7
Buffer	5-10
Imidazolidinyl urea	0.1
Lanolin alcohol	5
Mineral Oil	14
Polyethylene Glycol 200	5
Water (q.s.)	100

* "Laneth-15" is the polyethylene glycol ether of lanolin alcohol having an average ethoxyation value of 15.

Ingredi nt	Wt %
"Arquad HTL-8"*	2
Metronidazole	0.5 - 10
Buffer	10
Glycerin	5
Min ral Oil 70/80	3
"Lantrol AWS"**	2.5
Cetyl Alcohol	0.25
"Germaben II"***	1
Water (q.s.)	100
Propellants as needed	

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* "Arquad HTL-8" is a trademark of AKZO Chemical America, Chicago, Illinois, for a brand of 2-ethylhexyl dimethyl hydrogenated tallow ammonium chloride.

** "Lantrol AWS" is a trademark of Emery Industries, Inc., Linden, N.J. for a reaction product of lanolin oil with ethylene and propylene oxides to form the trade designated produce "PPG-12--PEG-65."

*** "Germaben II" is a trademark of Sutten Laboratories, Inc., Chatham, N.J. for a composition of propylene glycol, diazolidinyl urea, and methyl and propyl parabens.

Ingredient	Wt %
Metronidazole	0.5 - 10
Sorbitol, 70% solution in H_2O	25
Isopropyl Myristate	5
C tyl Alcohol	8
Glyc ryl stearate/PEG-100 stearate	5
White Petr latum	1
Benzyl Alcohol	1
Aqueous acetate buffer solution, pH 4.0 (q.s.)	100

O/W Composition VI

Ingredient	Wt %
Metronidazole	0.5 - 10
Glyceryl stearate/PEG-100 stearate	10
Isopropyl Myristate	10
Cetyl Alcohol	1
Methyl Paraben	0.1
Propyl Paraben	0.05
Glycerin	5
"Carbopol 934P" (2%)	10
Buffer salts	5 - 10
NaOH (2%)	10
Water (q.s.)	100

Composition I
(Ointment)

Ingredient	Wt %
Metronidazole	0.5 - 10
Propylen Glycol	5 - 10
PEG-400*	30 - 40
Potassium Phthalate) (suspended buffer)	0.1 - 5
PEG-8000** (q.s.)	100

* "PEG-400" is $H(OCH_2CH_2)_nOH$ where n has an approximate value of 400.

** "PEG-8000" is $H(OCH_2CH_2)_nOH$ where n has an approximate value of 8000.

Composition II
(Gel)

Ingredient	Wt %
Metronidazole	0.5 - 10
Propylene Glycol	5 - 10
Buffer salts	2 - 10
Hydroxypropyl cellulose	0.5 - 5
Methyl Paraben	0.1
Glycerin (q.s.)	100

Composition I
(Buffered Metronidazole G 1
Composition; Preferred Embodiment)

Ingredient	Wt %
Metronidazole	0.1 - 1
"Carbopol 934P"	1 - 2
Edetate Disodium	0.05
Propylene Glycol	0 - 15
Methyl Paraben	0.08
Propyl Paraben	0.02
NaOH 10% solution (q.s.)	pH 3.75 - 4.25
Water (q.s.)	100

A composition constituted by the buffer system and the physiologically tolerable medium, but without metronidazole, is also useful as a vaginal acidifier. Such a composition is illustrated below.

Composition II
(Buffered Vaginal Acidifier)
(Contains no Metronidazole)

Ingredient	Wt %
"Carbopol 934P"	1 - 5
Edetate Disodium	0.05
Propylene Glycol	0 - 15
Methyl Paraben	0.08
Propyl Paraben	0.02
NaOH 10% Solution (q.s.)	pH 3.75 - 4.25
Water (q.s.)	100

In addition to the above illustrated vaginal acidifier utilizing a gel as the physiologically tolerable medium for the buffer system that is present, the physiologically tolerable medium can be a

For the buff red vaginal acidifier the buffer system is selected so as to provide a buffered pH value in the range of about 3 to about 4.25, preferably in the range of about 3.75 to about 4.25.

Composition III

Ingredient	Wt %
Metronidazol	0.1 - 10
Methylcellulose 4000 cps	3
Propylene Glycol	1 - 5
Aqueous acetate buffer solution, pH 4.0 (q.s.)	100

Composition IV

Ingredient	Wt %
Metronidazole	0.1 - 1
"Polyquaternium-10"	2.5
Aqueous acetate buffer solution, pH 4.0 (q.s.)	100

Composition V
(Buffered Solution Administered as a Foam)

Base consists of an oil-in-water emulsion or an aqueous solution or an aqueous suspension of metronidazole and buffer components with a surfactant. The propellant causes the foam to emit preferably as a quick breaking or as a thick, rich foam.

Hydroxy thyl cellulose	0.5
M tronidazole	0.5 - 10
Propyl ne Glycol	5 - 15
Buffer salts, pH 4.0	10
"Kathon CG"*	0.1
Wat r (q.s.)	100

Propellant and foaming agent, as needed

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* "Kathon CG" is a trademark of Rohm and Haas Co., Inc., Philadelphia, PA for a brand of methylchloroisothiazolinone and methylisolthiazolinone mixture.

EXAMPLE 8: Vaginal Inserts/Suppositories

Composition I
(Oleaginous Suppository)

Oil base systems such as cocoa butter or mixtures of hydrogenated fats in which buffer salts are suspended.

Ingredient	Wt %
Metronidazole	0.5 - 10
Buffer salts	2 - 10
Colloidal silica	2
Cocoa Butter (q.s.)	100

This system contains mixtures of polyethylene glycols which dissolve in vaginal fluid. The buffer is dissolved or suspended in the P.E.G.

Ingredient	Wt %
Metronidazole	0.5 - 10
Buffer salts	2 - 10
"PEG-8000" (30%)	100
"PEG-1540" (70%)*	

* "PEG-1540" is $H(OCH_2CH_2)_nOH$ where n has a value of about 1540.

Composition III
(Glycerin and Glycerinated
Gelatin Based Suppositories)

A glycerin-based suppository contains metronidazole and the buffer system dissolved or suspended in approximately 85% - 90% glycerin with 5% to 10% sodium stearate. Glycerinated gelatin systems contain the drug and buffer components dissolved or suspended in glycerin and congealed with gelatin.

Ingredient	Wt %
Metronidazole	0.5 - 10
Buffer System	1 - 10
Glycerogelatin (q.s.)	100

(Vaginal Tablet/Insert)

This system includes a tablet admixture of the drug and buffer which dissolves in vaginal fluids.

Ingredient	Wt %
Metronidazole	0.5 - 10
Buffer System	10
Microcrystalline cellulose	1
Beta Lactose (q.s.)	100

EXAMPLE 9: The Buffering Effect of the Metronidazole Gel Formulation

To determine and demonstrate the effectiveness of the gel composition as a buffer, the following work was carried out:

Procedure:

The gel formulation delineated in Table I below was prepared by the procedure of Example 1 above except for sodium hydroxide addition as described herein, and such was then titrated by the addition of strong base. A titration was carried out on each of two separate batches of the formulation. In one case, the titrant was a concentrated aqueous solution of sodium hydroxide (2.5N). This solution increased the resulting total composition volume only about 8 cc. In the other case, a dilute solution of sodium hydroxide (0.1N) was used as the titrant, which resulted in a doubling of the resulting composition volume from about 100 cc to 200 cc. This procedure allowed an examination of the effects of dilution on the buffer strength of the product.

Metronidazole Gel Formulation

Component	Percent W/W
Metr nidaz le	0.75
Propylene Glycol	3.00
Propyl Paraben	0.02
Methyl Paraben	0.08
Disodium EDTA	0.05
Carbopol 934-P	1.60
Sodium Hydroxide	a
Distilled Water (q.s.)	100.00

[a]Sodium hydroxide was omitted from this formulation so that titration could be carried out.

Results:

The titration data that resulted using the 0.1N sodium hydroxide is presented in Table II below and shown in accompanying FIGURE 1. The pH range over which there is significant buffering is from about pH 4 to 7.5. The slope in this region is 0.228. The reciprocal of the slope, 4.39, is the buffer capacity. This means that 4.39 mEq of base are needed to change the pH by one unit. The slope in the pH range from 4.05 to 4.92 is 0.285 and the buffer capacity in this region is slightly less at 3.51. The slope in the pH range from 4.92 to 6.89 is 0.213 and the buffer capacity is 4.69.

The titration data using the 2.5N sodium hydroxide is presented in Table III and shown in FIGURE 2. Again there is a significant buffering effect over a pH range of about 4 to 7.5. The slope of the titration curve in this region is 0.230 and the buffer capacity is 4.36. The slope from pH 4.08 to 4.89 is 0.324 and the

pH 4.89 to 6.79 is 0.220 and the buffer capacity is 4.55. This data is very similar to th titration data using the more dilute titrant.

Conclusions:

1. There is a significant buffering effect by the components of the metronidazole gel formulation over a pH range of 4 to 7.5.

2. There is very little effect on the buffer strength of the formulation upon dilution. This is significant since the formulation will become diluted when used, but will not lose its ability to help prevent and treat the alkalinization of the environment caused by infections of the type treated by metronidazole.

Titration Data Using 0.1N Sodium Hydroxide

mEq of Base	pH	mEq of Base	pH
0	3.27	10.5	6.20
0.5	3.57	11.0	6.33
1.0	3.83	11.5	6.43
1.5	4.05	12.0	6.55
2.0	4.22	12.5	6.67
2.5	4.37	13.0	6.77
3.0	4.56	13.5	6.89
3.5	4.65	14.0	7.01
4.0	4.77	14.5	7.14
4.5	4.92	15.0	7.28
5.0	5.07	15.5	7.43
5.5	5.17	16.0	7.55
6.0	5.29	17.0	7.89
6.5	5.39	18.0	8.36
7.0	5.48	19.0	9.85
7.5	5.58	20.0	11.26
8.0	5.68		
8.5	5.79		
9.0	5.89		
9.5	6.00		
10.0	6.11		

Titration Data Using 2.5N Sodium Hydroxide

mEq of Base	pH	mEq of Base	pH
0	3.33	12.50	6.79
1.25	4.08	13.75	7.05
2.50	4.64	15.00	7.30
3.75	4.89	15.50	7.56
5.00	5.35	16.00	7.78
6.25	5.54	16.50	8.20
7.50	5.75	17.00	8.52
8.75	6.11	17.50	9.58
10.00	6.53	18.00	11.42
11.25	6.57		

EXAMPLES 10 and 11: Clinical Trials: BV

To investigate the effectiveness of the method of this invention for the treatment of BV, the following clinical trials were conducted:

Two groups of human female patients were established. One group was treated for three days; the second group was treated for seven days.

All patients participating in these trials were preliminarily evaluated and were diagnosed to have BV based on positive tests in each patient of at least three of the four standard clinical test criteria employed for diagnosis of BV, as follows:

(1) clue cells comprise at least 20% of vaginal epithelial cells;

(2) homogeneous vaginal discharge;

(3) vaginal pH is greater than or equal to 4.7; and

(4) fishy amine odor appears upon addition of 10% KOH to vaginal discharge.

based on a physical examination and stated medical history.

Only patients thus diagnosed to have solely BV were enrolled in these studies. Thus, patients who evidenced the presence of Candida or trichomoniasis vaginitis, whether concurrently with BV or not, were excluded, as were patients who were (a) involved in any concurrent antibiotic therapy for any condition within 14 days of the start of these studies, or (b) involved in the administration of any investigational drug within 30 days of the start of these studies. Also excluded were patients who had a history of hypersensitivity to metronidazole or to parabens, who were pregnant, who were nursing mothers, who were menstruating at the time of diagnosis, and/or who were unwilling to abstain from sexual intercourse during the treatment phase of the studies.

The vaginal gel used was prepared according to the procedure of Example 1 (above) and such contained 0.75 weight percent metronidazole. Five gram unit dose forms of the gel were administered on a twice daily basis in the morning and evening. Thus, each unit contained 37.5 mg of metronidazole.

Each patient was instructed to self-administer two unit doses daily, one in the morning, and one in the evening, for the assigned treatment period.

Each patient was examined at the end of her assigned treatment period. The presence of three of the above-indicated four standard clinical criteria for diagnosis of BV indicated a treatment failure. The lack of three of the above-indicated four standard clinical criteria for diagnosis of BV indicated a treatment success. Each patient was also examined for the presence of local or systemic adverse effects as a result of treatment.

In the seven-day treatment, of the 11 patients treated, a 100% success rate was observed.

No local or systemic adverse effects were report d in any patients during these trials.

Data from the three-day treatm nt series is shown in Tabl s IV and V below (see Table Headings).

Data from the seven-day treatment seri s is shown in Tables VI and VII below (see Table Headings).

TABLE IV

Vaginal pH Values for Bacterial Vaginosis Patients Treated for 3 Days with 0.75% Metronidazole Gel

	Vaginal pH			
Patient Number	(Baseline) Visit #1	Visit #2	Visit #3	Visit #4
1	5.5	4.0	4.5	4.5
2	5.5	4.5	3.5	4.5
3	5.5	4.5	4.5	Not taken
4	5.5	4.5	4.0	4.0
5	4.5	4.0	4.0	4.0
6	4.5	4.5	4.5	Terminated
7	4.5	4.0	4.5	Terminated
8	5.5	4.0	4.0	4.0
9	5.0	3.75[1]	4.25[2]	Not taken
10	5.5	4.0	4.0	5.5
n = 10	n = 10	n = 10	n = 10	n = 6
	$\bar{x}$ = 5.15	$\bar{x}$ = 4.18	$\bar{x}$ = 4.18	$\bar{x}$ = 4.42

[1] Reported as range 3.5 to 4.0.

[2] Reported as range 4.0 to 4.5.

Table V

Summary of Results on Bacterial Vaginosis
Patients Treated for 3 Days with 0.75% Metronidazole Gel

	Visit #2		Visit #3			Visit #4		
Patient Number	Days Since Baseline Visit	Treatment Success Or Failure	Days Since Last Visit	Days Since Baseline Visit	Treatment Success Or Failure	Days Since Last Visit	Days Since Baseline Visit	Treatment Success Or Failure
1	3	Success	17	20	Success*	14	34	Success#
2	4	Success	23	27	Success*	8	35	Success*
3	5	Success	11	16	Success*	18	34	Success*
4	7	Success	10	17	Success*	12	29	Success*
5	3	Success	14	17	Success*	18	35	Success*
6	4	Success	14	18	Failure*	--	--	--
7	3	Success	14	17	Failure*	--	--	--
8	4	Success	14	18	Success	12	30	Success*
9	4	Success	13	17	Success*	14	31	Success*
10	3	Success	14	17	Success*	16	33	Failure
n = 10	n = 10	10/10 Successes	n = 10	n = 10	8/10 Successes	n = 8	n = 8	7/10 Succes
	$\bar{x}$ = 4.0		$\bar{x}$ = 14.4	$\bar{x}$ = 18.4		$\bar{x}$ = 14.0	$\bar{x}$ = 32.6	
	(3-7 days)		(10-23 days)			(8-18 days)		

* Gram stain showed presence of Gram-positive rods indicative of Lactobacillus.

\# No Gram stain taken.

Vaginal pH Values for Bacterial Vaginosis Patients Treated for 7 Days with 0.75% Metronidazole Gel

Patient Number	Vaginal pH (Baseline) Visit #1	Visit #2	Visit #3	Comments
1	5.5	---	---	Dropped
2	5.0	4.5	4.5	
3	4.5	4.0	4.0	
4	5.5	4.0	4.0	
5	5.0	3.75[1]	4.0	
6	5.5	3.75[1]	3.5	
7	5.0	4.0	---	Dropped
8	5.5	4.0	4.0	
9	5.0	3.5	---	
10	5.5	4.0	4.5	
11	5.5	4.0	4.5	
12	>5.5	4.5	5.0	
13	4.5	4.0	4.5	
	n = 13	n = 12	n = 10	
	$\bar{x}$ = 5.2	$\bar{x}$ = 4.0	$\bar{x}$ = 4.3	

[1] Reported as a range: 3.5 to 4.0.

TABLE VII

Summary of Results on Bacterial Vaginosis
Patients Treated for 7 Days with 0.75% Metronidazole Gel

Patient Number	Age	Visit #2 Days Since Last Treatment Day	Treatment Success or Failure	Visit #3 Days Sinc Last Treatment Day	Treatment Success or Failure
1	25	0	Success	--°	---
2	20	0	Success*	8	Success*
3	22	0	Success	7	Success*
4	18	2	Success*	24	Success#
5	34	3	Success*	14	Succes *
6	36	3	Success	17	Succ ss*
7	20	10	Success	--+	---
8	24	3	Success*	18	Succ ss*
9	22	12	Success*	27	Success*
10	25	5	Success*	15	Success
11	19	2	Success*	14	Succ ss
12	21	1	Success*	13	Success*
13	23	1	Success*	15	Success#
n = 13	$\bar{x}$ = 23.8 years (18 to 36 years)	$\bar{x}$ = 3.2 days (0 to 12 days)	13/13 = Success	$\bar{x}$ = 15.6 days (7 to 27 days)	11/11 = Succ ss

° Dropped: Intrastudy treatment for chlamydia.
+ Dropped: Intrastudy treatment for Candida.
* Gram stain showed presence of Gram-positive rods indicative of Lactobacillus.
# Gram stain not taken.

Trichomonas Vaginalis Treatment

Using the gel composition of Example 1 above, two female patients who present d T. Vaginalis inf ctions were each treat d with a total dos of only 525 mg f metronidazole over a sev n day p riod. Each patient administer d a unit dose of 3.75 mg m tronidazole tw times daily.

One patient was considered a treatment success on the second follow-up examination at 11 days after the last treatment day.

The second patient was considered a treatment failure at the second follow-up examination at 18 days after the last treatment. Whether or not such failure was due to ineffective therapy and therefore a recurrence, or to reinfection from a sexual partner, was not determined.

Based on this encouraging limited data, it appears that the same combination of a low dose metronidazole delivered in a formulation that can adjust and maintain vaginal pH is useful in the treatment of T. vaginalis infections.

Table VIII

Summary of Results on Trichomoniasis
Patients Treated for 7 Days with 0.75% Metronidazole Gel

Patient Number (Age)	VISIT #2 Days Since Last Treatment Day	Treatment Success or Failure	VISIT #3 Days Since Last Treatment Day	Treatment Success or Failure
14 (39)	1	Success	18	Failure
15 (23)	4	Success	11	Success

illustrativ and is not to b taken as limiting. Still oth r variations within the spirit and the scope of th invention ar p ssible and will readily present themselves to those skilled in the art.

Bibliography:

Amsel R. Critchlow CW, Spi gel CA, Chen KCS, Eschenbach D, Smith K, Holmes KK. Edited by S.M. Finegold, W.L. Goerge and R.D. Rolfe. Comparison of metronidazole, ampicillin, and amoxicillin for the treatment of bacterial vaginosis (nonspecific vaginitis): possible explanation for the greater efficacy of metronidazole. Proceedings of the First U.S. Metronidazole Conference. Biomedical Information Corporation, 1982.

Amsel R, Critchlow CW, Spiegel CA, Chen KCS, Eschenbach D, Smith K, Holmes KK. "Comparison of metronidazole, ampicillin, and amoxicillin for treatment of bacterial vaginosis (nonspecific vaginitis): possible explanation for the greater efficacy of metronidazole." In proceedings of the First U.S. Metronidazole Conference: pp. 225-242. Edited by Finegold SM, George WL, and Rolfe RD. N.Y.: Biomedical Information Corporation, 1982.

Balsdon MJ, Pead L, Taylor GE, et al. "Corynebacterium vaginale and vaginitis: a controlled trial of treatment." Lancet 1, 501, 1980.

Bartlett JG, Polk BF. Bacterial flora of the vagina: quantitative study. Rev Infect Dis, (Suppl 1) 6, S67-S72, 1984.

Bistoletti P, Fredricsson B, Hagstrom B, Nord CE. "Comparison of oral and vaginal metronidazole therapy for nonspecific bacterial vaginosis." Gynecol Obstet Invest, 21, 144-149, 1986.

Centers for Disease Control. MMWR Supplement. "1985 STD treatment guidelines." Volume 34 (4S), October 18, 1985.

Charles D, Glover DD. Antimicrobial treatment of infectious vaginopathies. The Female Patient, 10, 25-42, 1985.

penetration into vaginal fluid by reversed-phase high-performance liquid chromatography. Am J. Obst t Gynec, 149, 802-803, 1984.

Eschenbach DA, Critchlow CW, Watkins H, Smith K, Spiegel CA, Chen KCS, Holmes KK. "A dose-duration study of metronidazole for the treatment of nonspecific vaginosis." Scand J Infect Dis, (Suppl) 40, 73-80, 1983.

Eschenbach DA, Hillier S, Critchlow C, Stevens C, DeRoven T, Holmes KK. Diagn sis and clinical manifestations of bacterial vaginosis. Am J of Obstet & Gynecol, 158, 819-829, 1988.

Fouts AL, Kraus SJ. Trichomonas vaginalis: reevaluation of its clinical presentation and laboratory diagnosis. J Infect Dis, 141, 137-143, 1980.

Hager WD, Brown ST, Kraus SJ, et al. Metronidazole for vaginal trichomoniasis: seven-day vs. single-dose regimens. JAMA, 244, 1219-1220, 1980.

Hagstrom B, Lindstedt J. "Comparison of two different regimens of metronidazole in the treatment of nonspecific vaginitis." Scand J Infect Dis, (Suppl) 40, 95-96, 1983.

Hill, LVH, Embil JA. Vaginitis: current microbiological & clinical concepts. Can Med Assoc J, 134, 321-331, 1986.

Larsen B, Galask RP. Vaginal microbial flora: composition and influence of host physiology. Ann Intern Med, 96, 926-930, 1982.

Malouf M, Fortier M, Morin G, Dube J-L. "Treatment of Hemophilus vaginalis vaginitis." Obstet Gynecol, 57 (6), 711-714, 1981.

Mardh P, Soltesy LV. In vitro interactions between Lactobacilli and other microorganisms occurring in the vaginal flora. Scand J Infect Dis, (Suppl) 40, 47-51, 1983.

McCue JD. Evaluation and management of vaginitis. Arch Intern Med, 149, 565-568, 1989.

Mead PB, Thomson JL, Ledger WJ, Eschenbach DA. "Establishing bacterial vaginosis." Contemp OB/GYN, 27, 186-203, February 1986.

vaginal epithelial cells: variables affecting adhesion and inhibition by m tronidazole. Genitourin Med, 61, 391-395, 1985.

Ph ifer TA, Forsyth PS, Durfee MA, Pollock HM, Holm s KK. "Nonspecific vaginitis: rol of Haemophilus vaginalis and treatment with m tronidazole." New Eng J Med, 298 (26), 1429-1434, 1978.

Purdon A, Hanna JH, Morse DL, et al. An evaluation of single d se metronidaz le treatment for Gardn rella vaginalis vaginitis. Obste Gynecol, 64, 271, 1984.

Rein MF. Vulvovaginitis and cervicitis, in Mandell GL, Douglas RG, Bennett TE (eds). Principles and Practice of Infectious Diseases, edition 2, New York, John Wiley & Sons Inc., pp. 729-738.

Robbie MO, Sweet RL. "Metronidazole use in obstetrics and gynecology: A review. Am. J. Obstet. Gynecol. 145, 865-881, 1983.

Skavin A, Sylwan J. Vaginal Lactobacilli inhibiting growth of Gardnerella vaginalis, mobiluncus and other bacterial species cultured from vaginal content of women with bacterial vaginosis. Acta Path Microbiol Immunol Scand, Section B, 94, 399-403, 1986.

Staerfelt F, Gundersen TJ, Halsos AM, Barlinn C, Johansen AG, Norregaard KM, Eng, J. A survey of genital infections in patients attending a clinic for sexually transmitted diseases. Scand J Infect Dis, 40, 53-57, 1983.

Swedberg J, Steiner JF, Deiss F, Steiner S, Driggers DA. "Comparison of single dose versus one week course of metronidazole for symptomatic bacterial vaginosis." JAMA, 258 (8), 1046-1049, 1985.

Totten PA, Amsel R, Hales J, Piot P, Holmes KK. Selective differential human blood filagen media for isolation of Gardnerella vaginalis. J Clin Microbiol, 15, 141-147, 1982.

1. A compositi n suitable for the treatment of vaginitis which contains metronidazole as the sole activ ingredient togeth r with a buffer system in a physi logically tol rable m dium; said buffer system being capable of providing a buffered pH value for the composition in the range of about 3 t about 4.25.

2. The c mposition of claim 1 wherein th quantity of metronidazole therein is at least about 0.1 weight percent on a total composition weight basis.

3. The composition of claim 1 wherein said buffered pH value is about 4.

4. The composition of claim 1 wherein said physiologically tolerable medium is an oil within which said buffer system and said metronidazole are suspended and/or dissolved.

5. The composition of claim 1 which is an emulsion selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions.

6. The composition of claim 1 which is anhydrous but water soluble.

7. The composition in accordance with claim 1 in a gel dosage form.

8. The composition in accordance with claim 1 in a suppository dosage form.

9. The composition in accordance with claim 1 in a tablet dosage form.

10. The composition in accordance with claim 1 in a foam dosage form.

11. The composition of claim 1 wherein said physiologically tolerable medium is water and said metronidazole and buffer system are dispersed therein.

12. The composition of claim 1 in the form of a unit dose containing metronidazole in an amount in the range of about 20 to about 500 milligrams.

viscosity at least sufficient to maintain said composition in a substantially non-fl wable state at ambient conditions.

14. The composition in accordanc with claim 1 wherein the buff r system present provides a buffered pH value in the range f about 3.75 to about 4.25.

15. A g l composition suitabl for intravaginal treatment of vaginitis comprising

metronidazole as the sole active ingredient dispersed in a gelled hydrophilic and water-dispersible polyacrylic acid polymer having free carboxylic acid groups and a molecular weight in the range of about 1,250,000 to about 4,000,000 daltons;

sufficient base to cause said composition to have a pH in the range of about 3.75 to about 4.25; and

an aqueous solvent for said metronidazole and said base.

16. The composition of claim 15 wherein the concentration of metronidazole present is at least about 0.1 percent by weight based on the total weight of said composition.

17. The composition of claim 15 wherein the concentration of metronidazole is in the range of about 0.25 percent to about 1.0 percent by weight based on the total weight of said composition.

18. The composition of claim 15 wherein the concentration of said metronidazole is about 0.75 percent by weight based on the total weight of said composition.

19. The composition of claim 15 wherein said polymer is present in a range of about 0.2 percent to about 7 percent by weight based on the total weight of said composition.

polymer is present in a range of about 0.5 percent to about 2.5 percent by weight based n the total w ight of said compositi n.

21. The composition f claim 15 wherein said polymer is present in an amount f about 2 percent by weight based n the total weight of said compositi n.

22. The composition of claim 15 wher in said gel composition further includes a solubilizer.

23. The composition of claim 18 wherein said solubilizer is propylene glycol and is present in an amount in the range of about 2 percent to about 5 percent by weight, based on the total weight of said composition.

24. The composition of claim 23 wherein said propylene glycol is present in an amount of about 3 percent by weight, based on the total weight of said composition.

25. The composition of claim 15 wherein said gel composition further includes a preservative.

26. The composition of claim 25 wherein said preservative includes at least one paraben.

27. The composition of claim 26 wherein said preservative consists essentially of methyl paraben present in an amount of about 0.08 weight percent and propyl paraben present in an amount of about 0.02 weight percent, based on the total weight of said composition.

28. The composition of claim 15 wherein said gel composition further includes ethylenediamine-tetra acetic acid in an amount in the range of about 0.01 percent to about 0.1 percent by weight, based on the total weight of said composition.

29. The composition of claim 15 in the form of a unit dose which contains about 20 to about 40 milligrams of said metronidazole.

of a unit dose which contains about 37.5 milligrams of metronidazole.

31. A vaginal acidifier composition consisting essentially of a buffer system in a physiologically tolerable medium; said buffer system being capable of providing a buffered pH value for the composition in the range of about 3 to about 4.25.

32. The vaginal acidifier composition in accordance with claim 31 wherein the physiologically tolerable medium is a gel.

33. The vaginal acidifier composition in accordance with claim 31 wherein the physiologically tolerable medium is a suppository.

34. The vaginal acidifier in accordance with claim 31 wherein the physiologically tolerable medium is a tablet.

35. The vaginal acidifier in accordance with claim 31 wherein the physiologically tolerable medium is a foam.

36. The vaginal acidifier in accordance with claim 31 wherein the physiologically tolerable medium is a cream.

37. A novel composition suitable for the treatment of vaginitis, substantially as described and exemplified herein.

38. A novel gel composition suitable for intravaginal treatment of vaginitis, substantially as described and exemplified herein.

39. A novel vaginal acidifier composition, substantially as described and exemplified herein.

DATED THIS 7 DAY OF JUNE 1990

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS